PROLONGED-RELEASE COMPOSITIONS COMPRISING TORASEMIDE AND A MATRIX-FORMING POLYMER

Field of the invention

This invention relates to prolonged-release diuretic compositions containing torasemide as active ingredient.

Brief description of the drawings

Figure 1 shows the curves of in-vitro release rate (cumulative values) of torasemide comparatively for immediate-release (IR) tablets and prolonged-release (PR) tablets according to Example 8.

Figure 2 shows the curves of in-vitro release rate of torasemide comparatively for immediate-release (IR) tablets and prolonged-release (PR) tablets according to Example 8.

Figure 3 shows the plasma concentration curves in man after administration of torasemide comparatively for immediate-release (IR) tablets and prolonged-release (PR) tablets according to Example 8.

Figure 4 shows the versus-time curves of the number of urinary urgencies in man after administration of torasemide comparatively for immediate-release (IR) tablets and prolonged-release (PR) tablets according to Example 8.

Background of the invention

Torasemide (US 4018929) is a potent diuretic with an extensive clinical use. Torasemide mainly acts by inhibiting sodium reabsorption in the ascending limb of Henle's loop (Puschett JB and Jordan LL. Mode of action of Torasemide in man. *Progress in Pharmacology and Clinical Pharmacology*. 1990;8(1):7-13). Torasemide interferes with $Na^{+}2C1^{-}K^{+}$ pump in the luminal cell membrane and blocks the basolateral chloride conductance (Greger R. Inhibition of active NaCl reabsortion in the thick ascending limb of the loop of Henle by torasemide. *Arzneim Forsch./Drug Res.* 1988;38(1):151-155).

The bioavailability for torasemide is 80-90% after oral administration, the kinetics is linear and the elimination half-life is 3-4 hours. The pharmacokinetic profile is characterized by a peak of maximum plasma concentration (C_{max}) which is reached within a rather short period of time (t_{max}: approximately 1 hour) and by a rapid elimination (t:approximately 3-4 hours) (Neugebauer G, Besenfelder E and Mollendorf E. Pharmacokinetics and metabolism of torasemide in man. *Arzneim Forsch./Drug Res.* 1988;38(1):164-166). Torasemide shows a linear dose-response relationship at doses from 2.5 to 20 mg for urinary volume. The sodium excretion exerts a minimal effect on potassium. (Scheen AJ. Doseresponse curve of torasemide in healthy volunteers. *Arzneim Forsch./Drug Res.* 1988;38(1):156-159; Barr WH et al. Torasemide dose-proportionality of pharmacokinetics and pharmacodynamics. *Progress in Pharmacology and Clinical Pharmacology.* 1990;8(1):29-37). The maximal effects on urine and electrolytes excretions are observed at approximately 2 hours after oral administration (Lesne M. Comparison of the pharmacokinetics and pharmacodynamics of torasemide and furosemide in healthy volunteers. *Arzneim Forsch./Drug Res.* 1988;38(1):160-163). All these effects clinically become apparent as an acute diuresis and by episodes of urinary urgency and suprapubic discomfort (Lambe R, Kennedy 0, Kenny M and Darragh A. Study of tolerance and diuretic properties of torasemide following oral or intravenous administration to healthy volunteers. *Eur J Clin Pharmacol* 1986; 31 (Suppl) : 9-14) .

Therefore, the availability of torasemide compositions, which may avoid the troublesome urinary urgencies caused by conventional immediate-release compositions is of a great interest.

Summary of the invention

An object of the present invention is to prepare diuretic compositions that may provide more stable plasma levels of torasemide in order to avoid the initial peak. This will provide a kinetic profile with fewer fluctuations and steadier levels. Thus, the frequency of urinary urgencies is reduced, which results in a greater comfort for patients who need treatment with torasemide.

The compositions of the present invention comprise torasemide, as active ingredient, and an excipient chosen from matrix-forming polymers, for example, polymers of acrylic acid, cellulose, glycerol behenate, guar gum, xanthan gum, chitosan, gelatin, polyvinyl alcohol and the like. In each composition one only polymer or a mixture thereof may be used. Other components that complete the compositions of the present invention are the usual excipients in pharmaceutical technology comprising diluents, for example, lactose, cellulose, mannitol, calcium phosphate and the like, as well as the mixtures thereof; binding- and disintegrating-action agents, for example,

fumed silica as AEROSIL® 200, starch, and the like, as well as the mixtures thereof; lubricants, for example, magnesium stearate, talc, and the like, as well as the mixtures thereof. Generally, the compositions of the present invention contain the active ingredient in a proportion from 0.5 to 20%, and the matrix-forming polymer in a proportion from 1 to 40%.

The compositions of the present invention are tablets for oral administration.

The compositions of the present invention maintain diuresis over a maximal period of 24 hours, preferably within the first 12 hours; thus, the possible disturbance of nocturnal enuresis is avoided. As the C_{max} of plasma levels attained after administration is minimal, the troublesome urinary urgency induced by immediate-release compositions is prevented.

Detailed description of the invention

The tablets of the present invention contain the active ingredient, torasemide, in an amount of 0.5 to 20 mg. In. practice, doses of 5, 10 and 20 mg per tablet are preferred. The matrix-forming polymers are chosen from the following groups: 1) acrylic polymers, for example, CARBOPOL® (a carbomer -a polymer of acrylic acid polymer), KOLLICOAT® SR 30 D (a Poly (Vinyl Acetate) dispersion stabilized with povidone and sodium lauryl sulphate), and their analogues and derivatives; 2) cellulose polymers, for example METHOCEL® (hydroxypropylmethylcellulose), methylcellulose, sodium carboxymethylcellulose, NATROSOL® (hydroxyethylcellulose) and their analogues and derivatives; 3) COMPRITOL® (glyceryl behenate); 4) MEYPROGAT® (guar gum) and its analogues and derivatives; 5) xanthan gum; 6) chitosan; 7) gelatin; and 8) polyvinyl alcohol and its derivatives.

The compositions of the present invention contain the active ingredient, torasemide, in a proportion from 0.5 to 20% and the matrix-forming polymer in a proportion from 1 to 40%. The most convenient matrix-forming polymer was found to be guar gum, preferably in a proportion of 4%. However, other matrix-forming polymers may be employed in the compositions; their proportions may be varied within a relatively wide range. Thus, CARBOPOL® is formulated at concentrations from 1 to 20%, preferably 10%, METHOCEL® at concentrations from 1 to 50%, preferably 40%, NATROSOL® and COMPRITOL® at concentrations from 1 to 40%, preferably 20%, KOLLICOAT® at concentrations from 1 to 40%, preferably 15% and MEYPROGAT® at concentrations from 1 to 40%, preferably 4%.

The tablets of the present invention are manufactured according to standard procedures of pharmaceutical technology by direct compression or by wet granulation in such a way that moisture of the resulting dry granulate is lower than 10%.

An *in vitro* dissolution test is performed on the tablets of the present invention using apparatus 2/paddle stirring element (according to U.S. Pharmacopeia) at 50 rpm.

In order to obtain a dissolution profile that fully models the physiological conditions, the test is performed within the first 2 hours at pH 1 and thereafter at pH 6.8. The results obtained are presented in Figures 1 and 2. Fig. 1 shows torasemide release (cumulative values) and Fig. 2 shows torasemide release.

The present invention is further illustrated by - but not 35 limited to - the following examples.

Example 1: 5 mg tablets of torasemide with CARBOPOL ® and a total weight of 85 mg

Torasemide	5.0 mg
CARBOPOL 940®	10.0 mg
Lactose	48.0 mg
Magnesium stearate	0.3 mg
AEROSIL® 200,	0.5 mg
Mannitol q.s.	85 mg

Example 2: 5 mg tablets of torasemide with METHOCEL® and a total weight of 100 mg

Torasemide	5.0 mg
METHOCEL K 15 M®	40.0 mg
Lactose	18.0 mg
Corn starch	36.2 mg
Pregelatinized starch	0.3 mg

AEROSIL® 200	0.5 mg

Example 3: 5 mg tablets of torasemide with NATROSOL® and a total weight of 85 mg

Torasemide	5.0 mg
NATROSOL HX®	20.0 mg
Magnesium stearate	0.3 mg
AEROSIL® 200	0.5 mg
Microcrystalline cellulose q.s.	85 mg

Example 4: 5 mg tablets of torasemide with COMPRITOL® and a total weight of 100 mg

Torasemide	5.0 mg
COMPRITOL 888®	20.0 mg
Lactose	38.0 mg
Corn starch	36.2 mg
Magnesium stearate	0.3 mg
Talc	0.5 mg

Example 5: 10 mg tablets of torasemide with KOLLICOAT ® and a total weight of 85 mg

Torasemide	10.0 mg
KOLLICOAT ® SR 30 D	30.0 mg
Magnesium stearate	0.6 mg
Talc	1.0 mg

Calcium phosphate q.s.	85 mg

Example 6: 5 mg tablets of torasemide with MEYPROGAT ® and a total weight of 100 mg

Torasemide	5.0 mg
MEYPROGAT ® 90	4.0 mg
Lactose	54.0 mg
Corn starch	36.2 mg
Magnesium stearate	0.3 mg
AEROSIL® 200	0.5 mg

Example 7: 5 mg tablets of torasemide with MEYPROGAT ® and a total weight of 85 mg

Torasemide	5.0 mg
MEYPROGAT ® 90	3.4 mg
Corn starch	30.77 mg
AEROSIL® 200	0.42 mg
Magnesium stearate	0.25 mg
Lactose	45.16 mg

Example 8: 10 mg tablets of torasemide with MEYPROGAT ® and a total weight of 170 mg

Torasemide	10.0 mg

MEYPROGAT ® 90	6.8 mg
Corn starch	61.54 mg
AEROSIL® 200	0.85 mg
Magnesium stearate	0.51 mg
Lactose	90.30 mg

Example 9: 20 mg tablets of torasemide with MEYPROGAT ® and a total weight of 340 mg

Torasemide	20.0 mg
MEYPROGAT ® 90	13.6 mg
Corn starch	123.08 mg
AEROSIL ® 200	1.70 mg
Magnesium stearate	1.02 mg
Lactose	180.6 mg

Example 10: Pharmacokinetics of torasemide in man

A randomized clinical trial was performed in a group of 10 healthy volunteers who were cross-administered with a 10 mg prolonged-release tablet of torasemide and a 10 mg immediate-release commercial tablet of torasemide (SUTRIL®, Novag, Spain). There was 1-week interval between the administration of each tablet. The prolonged-release torasemide composition exhibited a lower peak of plasma levels (C_{max}) attained less acutely (t_{max}) with steadier levels and fewer fluctuations (Fig. 3). The prolonged-release composition produced a lesser frequency of acute diuresis episodes than the immediate-release composition (Fig. 4).

These data show that the compositions of torasemide in the present invention produce a lower peak

of plasma levels and fewer fluctuations than the immediate-release composition. In addition, there is a shorter number of urinary urgency episodes after the prolonged-release torasemide composition.